

PATENT ABSTRACTS OF JAPAN

(11)Publication 05-194229

n number :

(43)Date of 03.08.1993

publication of

application :

(51)Int.Cl.

A61K 31/505

A61K 31/505

A61K 31/505

// C07D475/04

(21)Applicati 04-257964

on number :

(22)Date of 28.09.1992

filing :

(71)Applicant KANEGAFUCHI CHEM IND CO LTD

:

(72)Inventor : HANSUUKURISUTOFU

KURUTEIUSU

HAINRITSUHIIGEORUKU

MIYURUDONAA

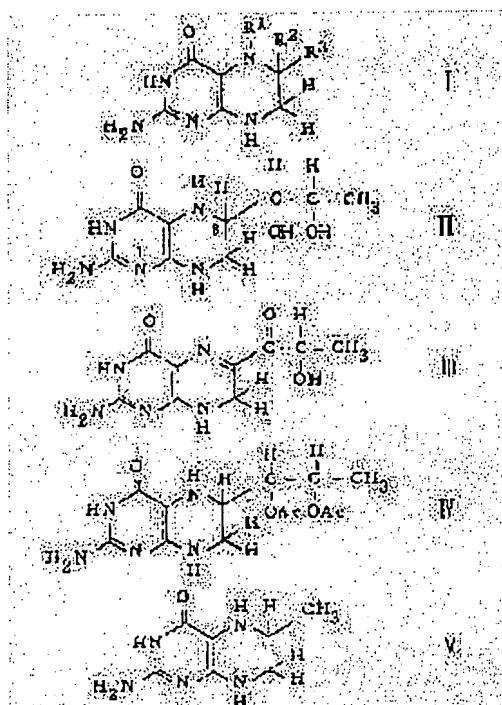
AAROISU NIIDAABIIZERU

(30)Priority

Priority number : 82 1300 Priority date : 03.03.1982 Priority country : CH

(54) NERVOUS DISEASE SYMPTOM-TREATING AGENT COMPRISING PTERIN
DERIVATIVE

(57)Abstract:



PURPOSE: To provide an agent for treating performance disorders, concentration disorders, paroxysmal anesthesia, akinesia, shivering or emotional unstable type atrabiliary symptom, i.e., nervous diseases, containing a specific pterin derivative as an active ingredient.

CONSTITUTION: A nervous disease-treating agent contains a compound of formula I [R¹, R² are H or together form a single bond; when R¹, R² are the H, R³ is -CH₃, L-erythro-CH(OH)CH(OH)CH₃, -CH(OCOCH₃)CH(OCOCH₃)CH₃; when R¹, R² are the single bonds, R³ is -COCH(OH)CH₃]. The compound of formula I includes L-erythro-5,6,7,8-tetrahydrobiopterin of formula II, L-sepiapterin of formula III, 1',2'-diacetyl-5,6,7,8-tetrahydrobiopterin of formula IV and 6-methyl-5,6,7,8-tetrahydropterin of formula V. These are effective for the treatment of Parkinson's disease patients and depression patients.

LEGAL STATUS

[Date of request for examination] 28.10.1992

[Date of sending the examiner's decision of rejection] 14.11.1995

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

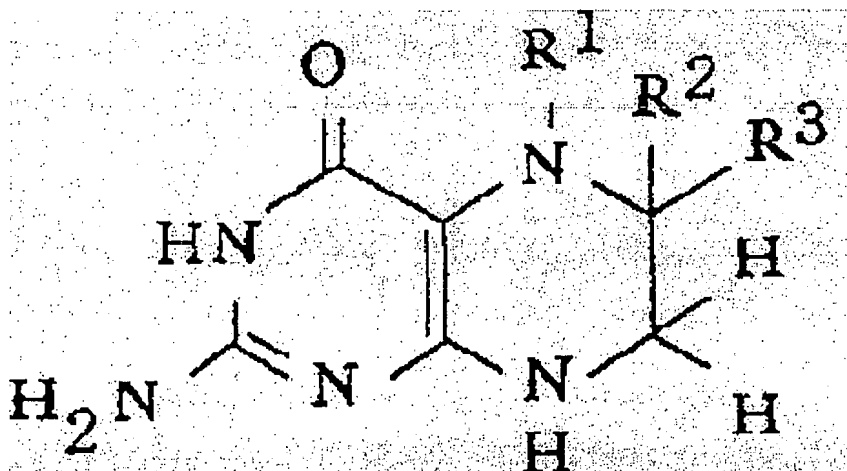
[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

Claim(s)]

[Claim 1] General formula [** 1]



When R₁ and R₂ show a hydrogen atom, respectively, or become one clue, single bond is shown among [type and R₁ and R₂ show a hydrogen atom R₃ shows -CH₃, L-erythro-CH(OH) CH(OH) CH₃, or -CH(OCOCH₃) CH(OCOCH₃) CH₃. R -- one -- and -- R -- two -- together -- becoming -- single bond -- being shown -- a case -- **** -- R -- three -- COCH -- (-- OH --) -- CH -- three -- being shown --] -- being shown -- having -- pterin -- a derivative -- a principal component -- ** -- carrying out -- actuation -- a failure -- concentration -- a failure -- spasmodic -- insensible (leisurely, inability, feeling of sadness) -- the akinesia -- a tremor -- or -- emotion -- uneasy -- a fixed form -- striking -- a symptom -- a therapy -- an agent .

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

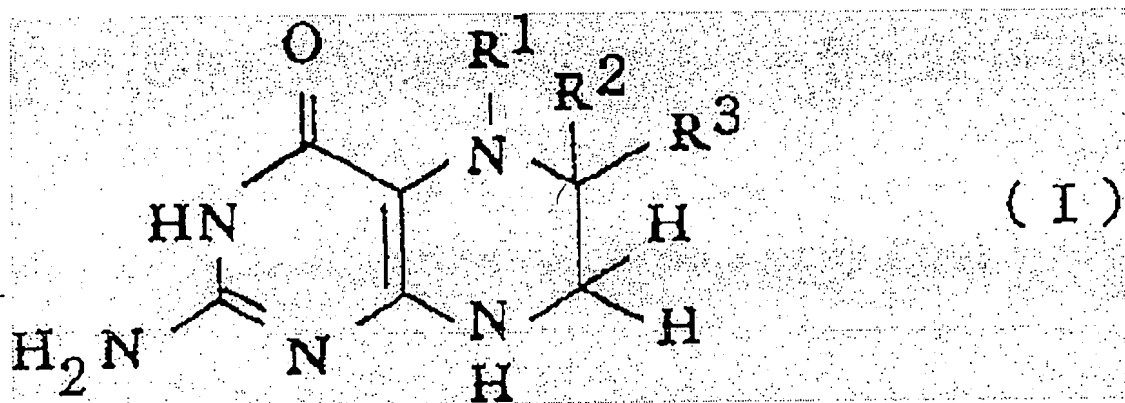
[Industrial Application] This invention relates to the therapy agent of the moral disease symptom which consists of a pterin derivative.

[0002]

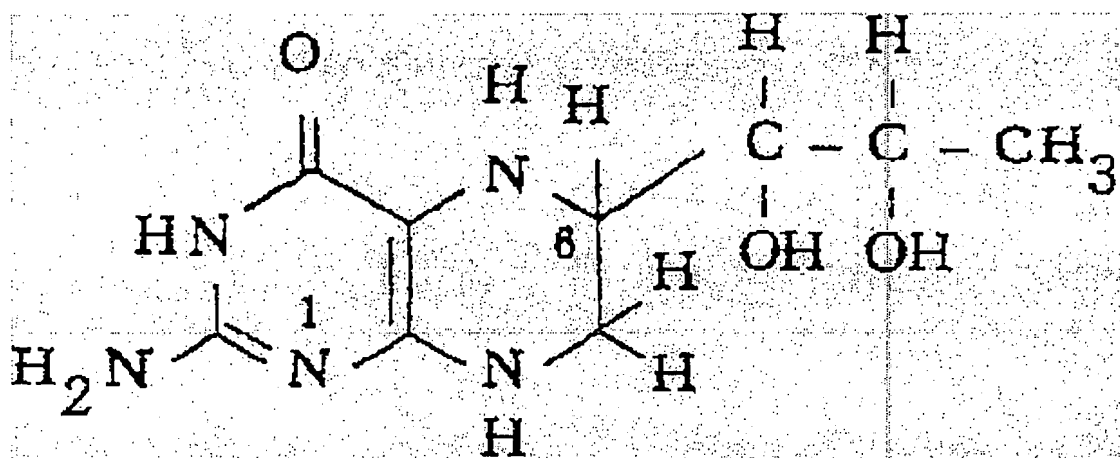
[Description of the Prior Art] L-erythro -- [V. Massey by whom it is known that -5, 6 and 7, and 8-tetrahydro biopterin are the natural coenzymes of phenylalanine 4-hydroxylase (enzyme number 1.14.16.1), tyrosine-3-hydroxylase (enzyme number 1.14.16.2), and tryptophan 5-hydroxylase (enzyme number 1.14.16.4), and P. HENRIHI "JI en ZAIMUSU" (volume for PD. Boyar) -- the 191 - 252nd page, and 3rd-edition Academic Press, Incorporated (New York) 1975 issue [12th-volume]]. Back 2 persons are important enzymes in the biosynthesis of neurotransmitter dopamine and serotonin.

[0003]

[Elements of the Invention] To a surprising thing, it is the following general formula [** 2].

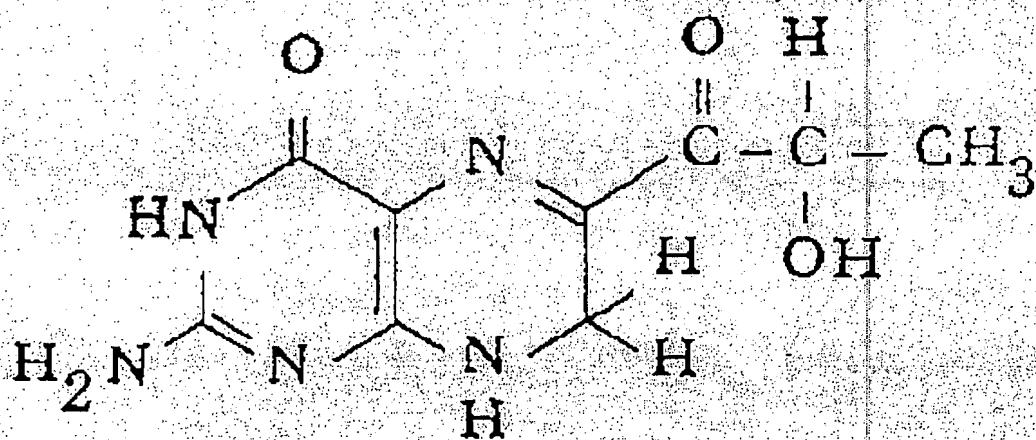


When R1 and R2 show a hydrogen atom, respectively, or become one clue, single bond is shown among [type and R1 and R2 show a hydrogen atom R3 shows -CH3, L-erythro-CH(OH) CH(OH) CH3, or -CH(OCOCH3) CH(OCOCH3) CH3. When R1 and R2 become together and single bond is shown R3 is the compound shown by] which shows -COCH(OH) CH3, i.e., L-erythro. - 5, 6, 7, 8-tetrahydro biopterin (it outlines the following BH 4), Sepia pterin, 1', 2'-diacetyl - 5, 6, 7, and 8-tetrahydro biopterin and 6-methyl - 5, 6, 7, 8-tetrahydro biopterin [** 3]



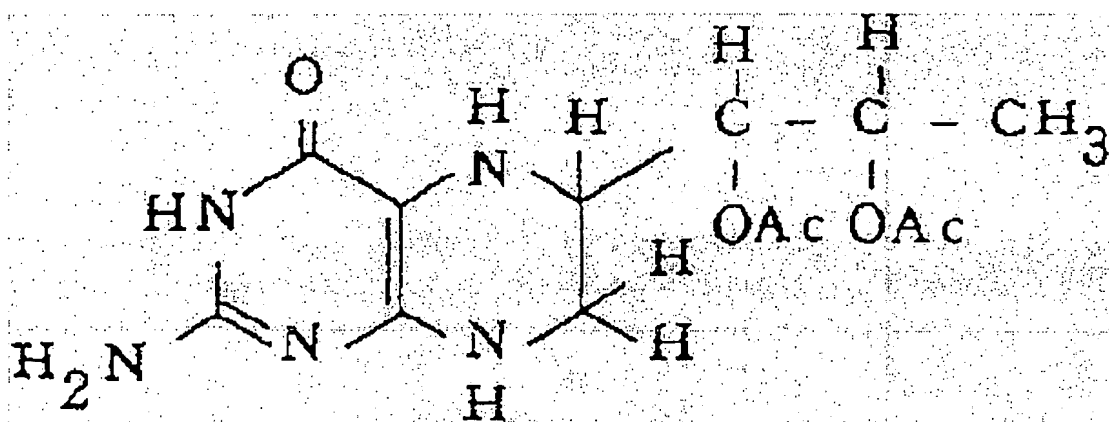
Ｌ－エリスロ－５，６，７，８－

テトラヒドロビオプテリン

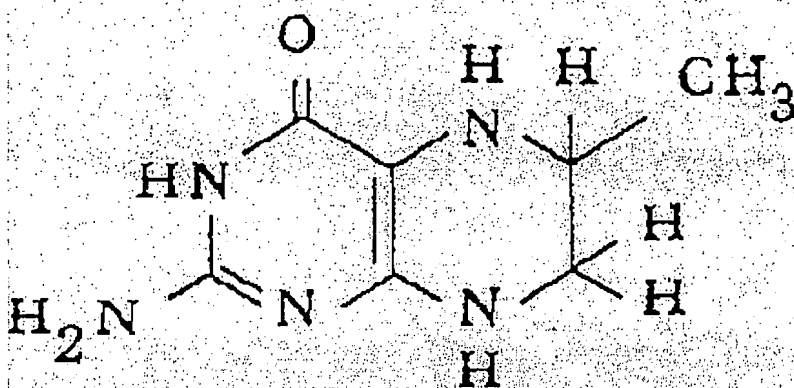


Ｌ－セピアプテリン

[Formula 4]



1, 2' - ジアセチル - 5, 6, 7, 8 -
テトラヒドロビオプテリン



6 - メチル - 5, 6, 7, 8 -
テトラヒドロプテリン

It became clear that it is effective in the therapy of **, a Parkinson's disease patient, and the melancholiac.

[0004] The pretreatment of all the patients of depression was carried out by the commercial antidepressant with the neuroleptic of versatility [part] again. Some patients did not react to the physic prescribed for the patient, and the clinical condition image did not change. If BH4 1g (what was stabilized to oxidization by adding 100mg of ascorbic acids) was put in and administered orally to Orange fruit juice, the clinical feature of

heavy depression will have been improved suddenly about 4 to 5 hours after. Similarly some other patients had received the pretreatment by the antidepressant. According to a rough clinical experience, these patients carried out the affirmative response to one antidepressant agent. Effectiveness appeared ordinarily for 1 thru/or three weeks. When medication was stopped, it returned to the original condition again. Then, when BH4 was prescribed for the patient as mentioned above, in contrast with the therapy by the old antidepressant, the clinical condition has been suddenly improved in a short time (4 to 5 hours). The side effect was not accepted. As for the ordinary side effect (thing of vegetation and drill outside-of-the-body nature) seen in the case of administration of the beginning of an antidepressant and neuroleptic, it happened at no time. It returned to the original condition again 12 thru/or 16 hours [the administration termination of BH4, and] after.

[0005] First, it is as follows when the symptoms of the inhibition depression type endogenous depression are shown.

1. Failure of Operation (Lack of Spontaneity of Moral Action Accompanied by Gradualizing of Movement Progress and Thinking Progress and Movement Action)
2. Concentration Failure 3. Spasmodic Numbness (Leisurely, Inability, Feeling of Sadness)

4. He is the 29-year-old male (familial genius) of the strong morning dissatisfied feeling
 5. somniphathy [loss weight 6.] (1) endogenous depression especially. The above-mentioned symptoms 1 thru/or 6 are all shown clearly, it is repeatedly [of a very strong loss weight and a depressed state], and these are not treated. There were unsociable wandering and advanced conamen during continuation of a disease. or [that symptoms 1, 2, and 3 will almost disappear 4 to 5 hours after even if it does not treat an antidepressant if BH4 is prescribed for the patient] -- or it no longer accepts. About symptoms 4, 5, and 6, since these should disappear for the first time after long duration, they are not indicated here.

(2) The 43-year-old male of the endogenous depression. A mother has the chronic melancholia and, in addition to symptoms as shown in (1), the guilt feeling is indicated. Sufficient result was not obtained, although it had been sent to hospital since ten years and the therapy by the antidepressant was undergone. The rapid improvement of a condition image appeared in the above forms after administration of BH4. The **ed Parkinson's disease patient received L-DOPA and the pretreatment by bromocriptine MEJIRATO (Parlodel, PURABIDERU), and the improvement of a clinical feature was found a little. The manifestation of the effectiveness by this treatment was checked six days after. In addition to the serious and rapid effectiveness manifestation, the nearly perfect improvement of the pain which exists was found in BH4.

[0006] Three symptoms characteristic of case Parkinson's disease are the akinesia (action which is gradual and imperfect and impresses spontaneity reduction of movement), a tremor (it is weak in the case of action and posture maintenance, and strong in the case of moral violent shaking), and a depressed state (emotion uneasy fixed form).

(1) The 72-year-old woman of idiopathic Parkinson's disease (familial genius). Remarkable symptoms are shown. Although most about 4 to 5 hours after [internal use] 3 syndromes of BH4 disappeared, such a result is not seen after the treatment by L-DOPA.

(2) The same progress was seen also when it dealt with the 62-year-old male of idiopathic

Parkinson's disease by BH4.

[0007] Moreover, effectiveness can also be proved biochemically. For example, the biopterin, dopamine, and serotonin of the concentration shown in the 1st table were detected in urine after medicating the patient binary name of the inhibition endogenous depression with tetrahydro biopterin and 2HCl(BH4) 1g, or diacetyl tetrahydro biopterin and 2HCl 0.9g.

[Table 1]

第 1 表						
各制止性うつ病患者にテトラヒドロbioプテリンまたはジアセチルテトラヒドロbioプテリンを経口投与後のbioプテリン、ドーパミン、セロトニン尿中排泄						
採尿時間(時間)	テトラヒドロbioプテリン・2HCl 1g投与後の濃度			1,2'-ジアセチルテトラヒドロbioプテリン・2HCl 0.9g投与後の濃度		
	bioプテリン(mmol/クレアチニンmol)	ドーパミン(μmol/クレアチニンmol)	セロトニン(μmol/クレアチニンmol)	bioプテリン(mmol/クレアチニンmol)	ドーパミン(μmol/クレアチニンmol)	セロトニン(μmol/クレアチニンmol)
0	0.36	1.47	3.0	0.90	7.8	2.4
2	1.36	2.08	4.2	0.77	1.80	3.4
4	6.71	2.20	6.0	1.13	2.00	5.7
8-10	6.04	2.20	4.0	-	-	-
12	0.91	2.10	3.4	0.82	5.8	6.1
正常範囲	0.31-1.09	7.0-17.0	2.2-6.0	0.31-1.09	7.0-17.0	2.2-6.0

The increment in the biopterin concentration in urine shows that the tetrahydro biopterin prescribed for the patient was absorbed in part at least, and that the ester group of diacetate was hydrolyzed inside. The above-mentioned table shows the original value of two sorts of neurotransmitter being in the field of the lower part of criteria partly, and having gone up during the treatment by tetrahydro biopterin or diacetyl tetrahydro biopterin. This has the improvement and parallel relation which were seen clinically.

[0008] It starts with the initial dose of 1g [day] (about 15mg / weight kg) order, for example, the therapy of Parkinson's disease or the melancholiac will be continued with the dose of 200mg (about 3 mg/kg)/day every day on the 2nd 500mg (about 7.5 mg/kg) and after the 3rd day. the constituents of this invention are a tablet, a pill, a capsule, powder material, liquids and solutions, and ****, corresponding to a desired medication method -- it can be made the administration gestalt of solid-states, such as a ** agent, or a liquid. Moreover, in addition to the compound of said general formula (I), a constituent can contain the physic of further others including the support for physic or the excipient used commonly.

[0009] The example shown below does not explain this invention and does not limit this. In addition, that it is with the active principle in an example shows one of the arbitration of the compound of a general formula (I).

Example 1 active principle 1g ascorbic acid 100mg Orange fruit juice 200ml above is mixed and it considers as liquids and solutions.

Example 2 active principle 100mg lactose 150mg above is mixed and a gelatin hard filled capsule is filled up.

Example 3 active principle 50mg corn starch 50mg lactose 150mg above is mixed and tableted and it considers as a tablet.

TECHNICAL FIELD

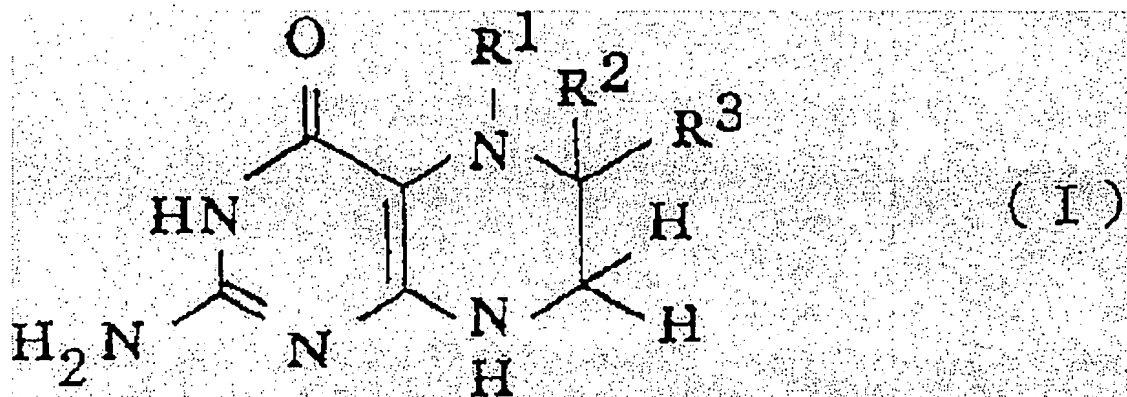
[Industrial Application] This invention relates to the therapy agent of the moral disease symptom which consists of a pterin derivative.

PRIOR ART

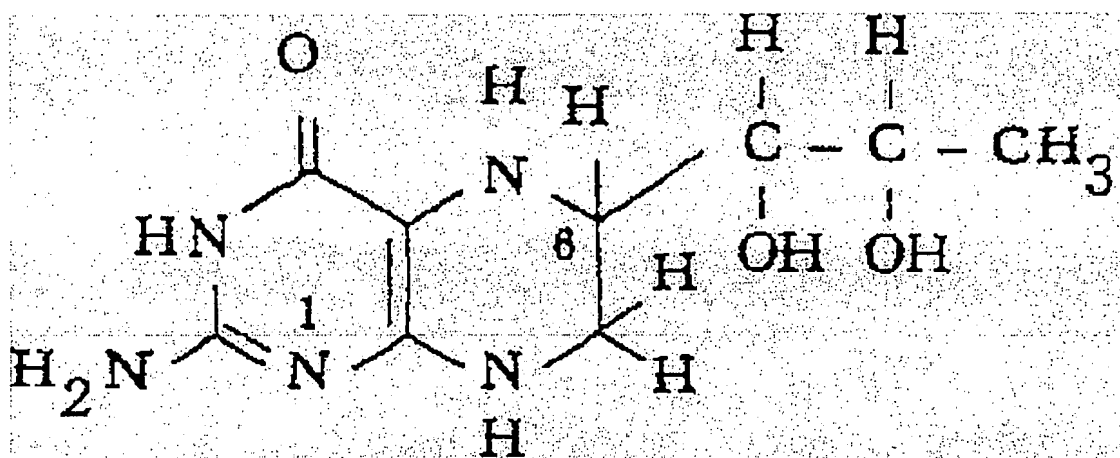
[Description of the Prior Art] L-erythro -- [V. Massey by whom it is known that -5, 6 and 7, and 8-tetrahydro biopterin are the natural coenzymes of phenylalanine 4-hydroxylase (enzyme number 1.14.16.1), tyrosine-3-hydroxylase (enzyme number 1.14.16.2), and tryptophan 5-hydroxylase (enzyme number 1.14.16.4), and P. HENRIHI "JI en ZAIMUSU" (volume for PD. Boyar) -- the 191 - 252nd page, and 3rd-edition Academic Press, Incorporated (New York) 1975 issue [12th-volume]]. Back 2 persons are important enzymes in the biosynthesis of neurotransmitter dopamine and serotonin.

[0003]

[Elements of the Invention] To a surprising thing, it is the following general formula [** 2].

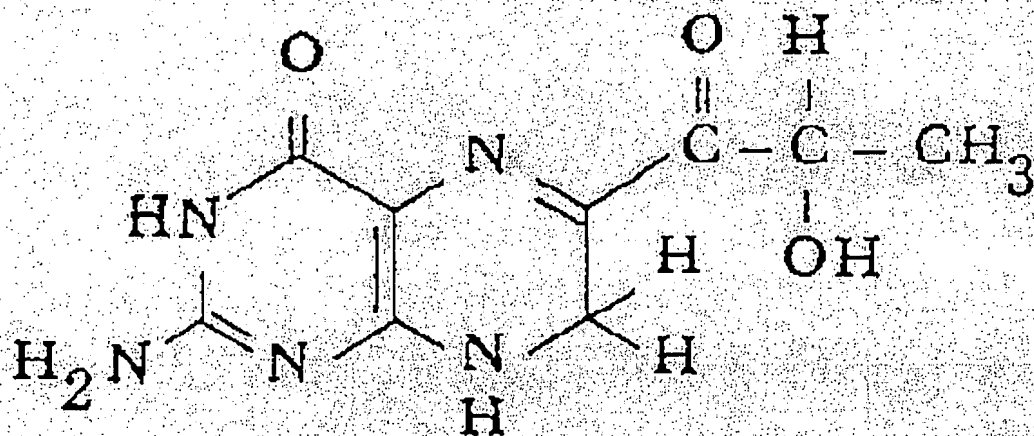


When R1 and R2 show a hydrogen atom, respectively, or become one clue, single bond is shown among [type and R1 and R2 show a hydrogen atom R3 shows -CH3, L-erythro-CH(OH) CH(OH) CH3, or -CH(OCOCH3) CH(OCOCH3) CH3. When R1 and R2 become together and single bond is shown R3 is the compound shown by] which shows -COCH(OH) CH3, i.e., L-erythro. - 5, 6, 7, 8-tetrahydro biopterin (it outlines the following BH 4), Sepia pterin, 1', 2'-diacetyl - 5, 6, 7, and 8-tetrahydro biopterin and 6-methyl - 5, 6, 7, 8-tetrahydro biopterin [** 3]



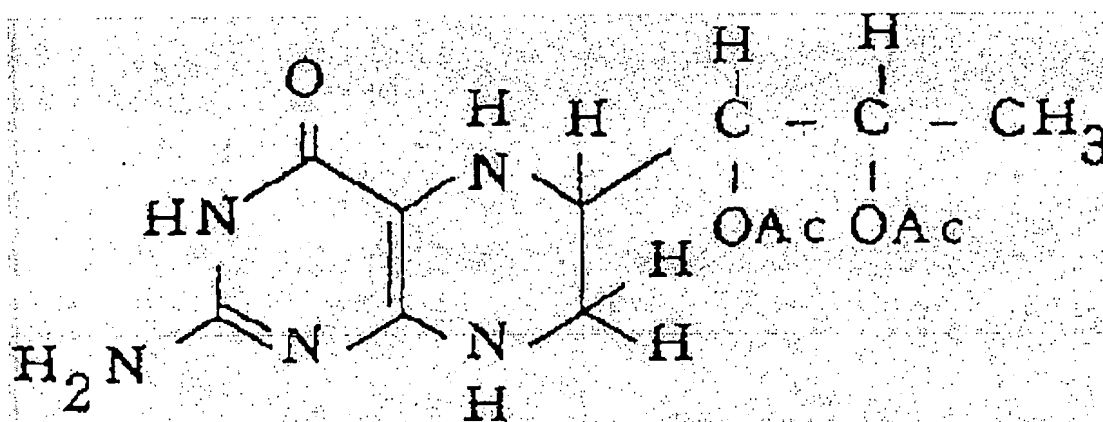
Ｌ－エリスロ－５，６，７，８－

テトラヒドロビオプテリン



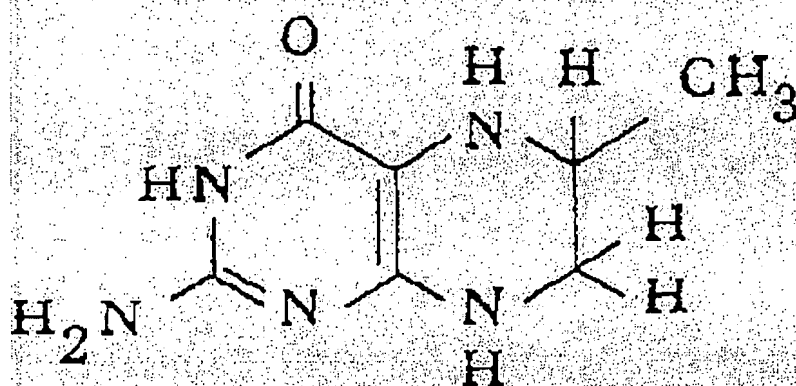
Ｌ－セピアプテリン

Formula 4]



1, 2' - ジアセチル - 5, 6, 7, 8 -

テトラヒドロビオプテリン



6 - メチル - 5, 6, 7, 8 -

テトラヒドロプテリン

It became clear that it is effective in the therapy of **, a Parkinson's disease patient, and the melancholiac.

[0004] The pretreatment of all the patients of depression was carried out by the commercial antidepressant with the neuroleptic of versatility [part] again. Some patients did not react to the physic prescribed for the patient, and the clinical condition image did not change. If BH4 1g (what was stabilized to oxidization by adding 100mg of ascorbic acids) was put in and administered orally to Orange fruit juice, the clinical feature of

heavy depression will have been improved suddenly about 4 to 5 hours after. Similarly some other patients had received the pretreatment by the antidepressant. According to a rough clinical experience, these patients carried out the affirmative response to one antidepressant agent. Effectiveness appeared ordinarily for 1 thru/or three weeks. When medication was stopped, it returned to the original condition again. Then, when BH4 was prescribed for the patient as mentioned above, in contrast with the therapy by the old antidepressant, the clinical condition has been suddenly improved in a short time (4 to 5 hours). The side effect was not accepted. As for the ordinary side effect (thing of vegetation and drill outside-of-the-body nature) seen in the case of administration of the beginning of an antidepressant and neuroleptic, it happened at no time. It returned to the original condition again 12 thru/or 16 hours [the administration termination of BH4, and] after.

[0005] First, it is as follows when the symptoms of the inhibition depression type endogenous depression are shown.

1. Failure of Operation (Lack of Spontaneity of Moral Action Accompanied by Gradualizing of Movement Progress and Thinking Progress and Movement Action)

2. Concentration Failure 3. Spasmodic Numbness (Leisurely, Inability, Feeling of Sadness)

4. He is the 29-year-old male (familial genius) of the strong morning dissatisfied feeling

5. somniphobia [loss weight 6.] (1) endogenous depression especially. The above-mentioned symptoms 1 thru/or 6 are all shown clearly, it is repeatedly [of a very strong loss weight and a depressed state], and these are not treated. There were unsociable wandering and advanced conamen during continuation of a disease. or [that symptoms 1, 2, and 3 will almost disappear 4 to 5 hours after even if it does not treat an antidepressant if BH4 is prescribed for the patient] -- or it no longer accepts. About symptoms 4, 5, and 6, since these should disappear for the first time after long duration, they are not indicated here.

(2) The 43-year-old male of the endogenous depression. A mother has the chronic melancholia and, in addition to symptoms as shown in (1), the guilt feeling is indicated. Sufficient result was not obtained, although it had been sent to hospital since ten years and the therapy by the antidepressant was undergone. The rapid improvement of a condition image appeared in the above forms after administration of BH4. The **ed Parkinson's disease patient received L-DOPA and the pretreatment by bromocriptine MEJIRATO (Parlodel, PURABIDERU), and the improvement of a clinical feature was found a little. The manifestation of the effectiveness by this treatment was checked six days after. In addition to the serious and rapid effectiveness manifestation, the nearly perfect improvement of the pain which exists was found in BH4.

[0006] Three symptoms characteristic of case Parkinson's disease are the akinesia (action which is gradual and imperfect and impresses spontaneity reduction of movement), a tremor (it is weak in the case of action and posture maintenance, and strong in the case of moral violent shaking), and a depressed state (emotion uneasy fixed form).

(1) The 72-year-old woman of idiopathic Parkinson's disease (familial genius).

Remarkable symptoms are shown. Although most about 4 to 5 hours after [internal use] 3 syndromes of BH4 disappeared, such a result is not seen after the treatment by L-DOPA.

(2) The same progress was seen also when it dealt with the 62-year-old male of idiopathic

Parkinson's disease by BH4.

[0007] Moreover, effectiveness can also be proved biochemically. For example, the biopterin, dopamine, and serotonin of the concentration shown in the 1st table were detected in urine after medicating the patient binary name of the inhibition endogenous depression with tetrahydro biopterin and 2HCl(BH4) 1g, or diacetyl tetrahydro biopterin and 2HCl 0.9g.

[Table 1]

第 1 表						
各制止性うつ病患者にテトラヒドロbiopterinまたはジアセチルテトラヒドロbiopterinを経口投与後のbiopterin、ドーパミン、セロトニン尿中排泄						
採尿時間(時間)	テトラヒドロbiopterin・2HCl 1g投与後の濃度			1,2'-ジアセチルテトラヒドロbiopterin・2HCl 0.9g投与後の濃度		
	biopterin (nmol / creatinine nmol)	dopamine (μmol / creatinine nmol)	serotonin (μmol / creatinine nmol)	biopterin (nmol / creatinine nmol)	dopamine (μmol / creatinine nmol)	serotonin (μmol / creatinine nmol)
0	0.36	1.47	3.0	0.90	7.8	2.4
2	1.36	2.08	4.2	0.77	18.0	3.4
4	6.71	2.20	6.0	1.13	20.0	5.7
8-10	6.04	2.20	4.0	-	-	-
12	0.91	2.10	3.4	0.82	5.8	6.1
正常範囲	0.31-1.09	7.0-17.0	2.2-6.0	0.31-1.09	7.0-17.0	2.2-6.0

The increment in the biopterin concentration in urine shows that the tetrahydro biopterin prescribed for the patient was absorbed in part at least, and that the ester group of diacetate was hydrolyzed inside. The above-mentioned table shows the original value of two sorts of neurotransmitter being in the field of the lower part of criteria partly, and having gone up during the treatment by tetrahydro biopterin or diacetyl tetrahydro biopterin. This has the improvement and parallel relation which were seen clinically.

[0008] It starts with the initial dose of 1g [day] (about 15mg / weight kg) order, for example, the therapy of Parkinson's disease or the melancholiac will be continued with the dose of 200mg (about 3 mg/kg)/day every day on the 2nd 500mg (about 7.5 mg/kg) and after the 3rd day. the constituents of this invention are a tablet, a pill, a capsule, powder material, liquids and solutions, and ****, corresponding to a desired medication method -- it can be made the administration gestalt of solid-states, such as a ** agent, or a liquid. Moreover, in addition to the compound of said general formula (I), a constituent can contain the physic of further others including the support for physic or the excipient used commonly.

[0009] The example shown below does not explain this invention and does not limit this. In addition, that it is with the active principle in an example shows one of the arbitration of the compound of a general formula (I).

Example 1 active principle 1g ascorbic acid 100mg Orange fruit juice 200ml above is mixed and it considers as liquids and solutions.

Example 2 active principle 100mg lactose 150mg above is mixed and a gelatin hard filled capsule is filled up.

Example 3 active principle 50mg corn starch 50mg lactose 150mg above is mixed and tableted and it considers as a tablet.